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Propranolol in the Treatment of Essential Hypertension

Veterans Administration Cooperative Study Group on Antihypertensive Agents

• In a series of 450 patients with mild essential hypertension, propranolol alone (P), propranolol plus hydrochlorothiazide (P+T), propranolol plus hydralazine (P+H), and propranolol plus hydrochlorothiazide plus hydralazine (P+T+H) were compared to reserpine plus hydrochlorothiazide (R+T). Comparison was based on reduction of diastolic blood pressures (BP) to below 90 mm Hg and at least 5 mm Hg less than initial BP after six months of treatment. This was achieved in 92% of patients who received P+T+H, 88% taking R+T, 81% receiving P+T, 72% on P+H and 52% taking P alone. The number of drop-outs, morbid events, and terminating side effects were insignificantly different among the various regimens. In this study, P and P+H were less effective, while P+T and P+T+H were as effective as the standard regimen.

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THE VETERANS Administration Cooperative Study Group on Antihypertensive Agents has demonstrated under controlled conditions the efficacy of reserpine, hydralazine hydrochloride, and the thiazide diuretics as antihypertensive agents when used alone or in combination.[1] The effectiveness of the ganglionic blocking drugs also was demonstrated in patients with more severe hypertension.[2] In later studies, the beneficial effects of antihypertensive drugs in reducing morbidity and mortality from hypertensive cardiovascular disease was demonstrated first for patients with diastolic arterial pressures between 114 and 129 mm Hg[3] and later in patients with diastolic blood pressures in the range of 90 to 114 mm Hg.[4]

Over the years, the Cooperative Study Group tested combinations of three commonly used drugs: hydrochlorothiazide, reserpine, and hydralazine, without assessing the value of other antihypertensive agents reported to be effective. One such drug is propranolol hydrochloride, a β-adrenergic blocking drug that was introduced more than a decade ago as an effective agent in the treatment of hypertension, first in Europe[5] and subsequently in this country.[6]

Propranolol has been reported to be effective in the treatment of essential hypertension of varying severity and of renovascular hypertension,[6] as well as labile hypertension, systolic hypertension, hypertension associated with hyperkinetic circulatory states,[7] and in patients with high renin hypertension.[8] In addition to suppression of an elevated renin secretion rate,[8] another proposed mechanism for the antihypertensive effect of propranolol has been a prolonged reduction of cardiac output with a secondary adaptation of the resistance vessels to the reduced cardiac output.[6]

Since propranolol blocks reflex adrenergic stimulation of the heart, it has been suggested as an adjunct to hydralazine. The latter drug reduces blood pressure primarily by peripheral arteriolar dilation that secondarily produces a reflex tachycardia and increase in myocardial contractility, thereby raising cardiac output. Combining hydralazine with propranolol, therefore, provides a physiological inhibition of the two major factors that raise arterial blood pressure—increased peripheral resistance and elevated cardiac output.

Although propranolol has been shown to reduce blood pressure, its relative effectiveness in comparison with a standard regimen such as a thiazide plus reserpine has not yet been demonstrated in adequate double-blind, controlled studies. This study was undertaken to assess the effectiveness of propranolol used alone and in combination, as compared to a standard regimen of hydrochlorothiazide and reserpine.

METHODS

Men between the ages of 18 and 59 years, whose diastolic blood pressures were in the range of 90 to 114 mm Hg, were recruited in the admitting room, outpatient clinics, and among hospitalized patients.

Excluded from the trial were patients with a history or findings of grade III or IV hypertensive neuroretinopathy, cerebral hemorrhage, dissecting aneurysm of the aorta, atrial fibrillation, a serum creatinine level greater than 2 mg/dl, or surgically curable hypertension. Also excluded were patients with sinus bradycardia of fewer than 60 beats per minute on two successive visits, patients with greater than first-degree heart block, congestive heart failure, asthma, or obstructive lung disease with cor pulmonale or asthmatic wheezes. Additional exclusions were patients with collagen vascular disease, a history of depression, or active duodenal ulcer. Patients desiring to return to their private physician or those who found it difficult to return to the clinic because of geographical location, as well as alcoholics or other potentially unreliable patients were excluded.

From participating Veterans Administration hospitals in Washington, DC; Jackson, Miss; Allen Park, Mich; Memphis; Miami; San Juan, PR; and Richmond, Va.

For a complete list of participants, see p 2310.

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Prerandomization Trial Period

Prior therapy was discontinued for at least four weeks before patients entered the prerandomization trial period. The nature of the study was explained to the patient, and written informed consent was obtained. (This study was approved by the Human Use Committee at each hospital and conformed to the principles of the Helsinki declaration.) A history was then taken and a physical examination performed. Chest roentgenogram, ECG, complete blood cell count, urinalysis, fasting blood glucose values, and serum determinations of potassium, uric acid, cholesterol, and creatinine were obtained. In addition, SGOT and alkaline phosphatase were determined as indexes for drug toxicity. A check list of the known side effects associated with the administered drugs was reviewed at each patient visit.

Blood pressure readings were taken on the right arm by means of an automated device (Arteriosonde 1010 [Roche]) three times each in the supine, sitting, and standing positions. The supine blood pressures were taken first after 10 to 15 minutes of undisturbed rest. The sitting and standing pressures were taken two minutes after each change of position. Unless otherwise stated, the diastolic blood pressures are the average of three fifth-phase (Korotkoff) readings taken in a sitting position. Pulse rate was determined after completion of blood pressure measurement in each position.

The patient entered a prerandomization trial period with procedures similar to those used during the actual trial period. The purposes of this prerandomization trial period were to determine the following: (1) the average pretreatment level of blood pressure, (2) whether it was in the range of acceptability for entering the trial, and (3) to test patient compliance. The patient was given two different bottles containing placebos identical in appearance to the drugs used in the actual trial period. One of these placebos contained riboflavin, 5 mg, which produces a yellow fluorescence under ultraviolet light when excreted into the urine. Both pill counts and urinary fluorescence were used as indexes of the patient's compliance. The patient was instructed to take one tablet from each bottle three times daily including his clinic visit day. He was further instructed to return bottles of remaining pills to the clinic on each visit.

A maximum of four biweekly visits was allowed to fulfill these requirements. The patient was included in the study if the average of diastolic blood pressures on two successive clinic visits was in the range of 90 to 109 mm Hg and he had no pill count or urine fluorescence violations on either of these visits. The patient was excluded from the study if the diastolic blood pressure was greater than 114 mm Hg at any prerandomization visit.

Table 1.—Double-Blind Trial Regimens*

	"Propaserp"	"Hydrazide"
R+T	Reserpine, 0.1 mg	Hydrochlorothiazide, 35 mg
P	Propranolol hydrochloride, 40,80,120,160 mg	Placebo
P+T	Propranolol, 40,80,120,160 mg	Hydrochlorothiazide, 35 mg
P+H	Propranolol, 40,80,120,160 mg	Hydralazine hydrochloride, 35 mg
P+T+H	Propranolol, 40,80,120,160 mg	Hydrochlorothiazide, 35 mg and hydralazine, 35 mg

*Because of the large numbers of patients with initial diastolic blood pressures in the 90- to 94-mm Hg range, only patients with diastolic levels greater than 94 mm Hg were included during the last six months of the recruitment period. These numbered 58.

Postrandomization Period

The study was designed as a double-blind trial. One of five regimens was randomly assigned to each patient who qualified for entry. These regimens are shown in Table 1. The propranolol-reserpine component was named "propaserp," while the hydralazine - hydrochlorothiazide - placebo component was named "hydrazide."

Each "propaserp" tablet was identical in appearance and taste to "hydrazide" tablet. On the day of randomization the patient was assigned the next consecutive number and was given a bottle of each of the two medications with the same instructions as in the prerandomization period. Clinic visits were scheduled on a monthly basis for six months, then were scheduled every two months until the study was completed.

During the postrandomization period, if diastolic blood pressures taken at any clinic visit were above 89 mm Hg or not less than 5 mm Hg below baseline, propranolol hydrochloride was increased by increments of 40 mg three times daily until a maximum dosage of 160 mg three times daily was attained. However, the reserpine dose was kept at 0.1 mg, and placebo was administered to simulate an increase in the propaserp dose. The investigators, therefore, did not know whether they were increasing the dose of propranolol or only maintaining a constant dose of reserpine.

"Hydrazide" therapy could not be increased beyond the initial dosage of one tablet three times daily, but dosages of propaserp or hydrazide could be reduced, and hydrazide could be omitted if the patient experienced hypotensive reactions. Pill counts and urine fluorescence analysis were carried out on each visit throughout the study.

To compare automated device readings against those of the standard auscultatory method, the blood pressure was also checked with a standard mercury sphygmomanometer, three times each in the supine, sitting, and standing positions at the time of randomization as well as at the 5-, 6-, 12-, and 18-month clinic visits. Systolic time intervals were also recorded at periodic intervals, the results of which will be reported in a separate communication.

Participation in the study was terminated if any of the following events occurred:

1. During the first six months following randomization, if the diastolic blood pressures exceeded 114 mm Hg on two visits two weeks apart after the dose had been titrated to the maximal permitted dose of "propaserp." Following the first six months, if the diastolic blood pressure exceeded 104 mm Hg on two successive clinic visits. This was considered termination for ethical reasons.
2. If there were hypotensive symptoms with a diastolic blood pressure under 90 mm Hg when the patient was receiving the minimal allowed dose of "propaserp."
3. If the patient failed to take protocol medications for three weeks consecutively or longer.
4. If there was symptomatic or persistent bradycardia—heart rate less than 40 beats per minute.
5. If the patient got bronchial asthma.
6. If congestive heart failure developed.
7. If there was peripheral vascular insufficiency or Raynaud phenomenon.
8. If the patient suffered depression confirmed by a psychiatrist.
9. If gastrointestinal bleeding or peptic ulcer developed.
10. If the patient developed arthralgia, dermatitis, or symptoms suggesting lupus erythematosus, with either lupus cells or a positive antinuclear antibody test.
11. If there were major cardiovascular complications of hypertension or atherosclerosis, involving either the central nervous system, heart, aorta or kidneys.

These were detailed in the protocol and are available by writing to the chairman of the study (Dr Thomas).

RESULTS

Of the 778 patients who entered the prerandomization trial period, 450 (58%) were included in the study, while 328 (42%) were dropped. Of the latter, 200 were noncompliant as judged by pill counts and urine fluorescence tests. Diastolic blood pres-

Table 2.—Mean (SE) Characteristics of 450 Patients at Time of Randomization*

	R+T	P	P+T	P+H	P+T+H
Age, yr	47.9(0.8)	47.8(0.8)	46.9(0.8)	48.0(0.9)	47.8(0.8)
Weight, kg	86.3(3.2)	82.8(2.8)	84.4(3.2)	86.2(3.1)	85.4(3.3)
Blood pressure, mm Hg					
Systolic					
Auscultation†	150.9(1.3)	151.2(1.6)	150.1(1.5)	150.7(1.6)	150.2(1.4)
Arteriosonde	151.2(1.4)	152.1(2.0)	151.9(1.6)	152.9(1.7)	152.1(1.7)
Diastolic					
Auscultation	97.4(0.5)	98.2(0.5)	97.4(0.5)	97.7(0.5)	97.7(0.6)
Arteriosonde	102.7(0.8)	104.2(0.9)	102.8(0.8)	103.1(0.8)	103.2(0.9)
Heart rate, beats per minute	77.4(1.1)	79.7(1.3)	78.7(1.1)	78.2(1.0)	78.2(1.0)
Uric acid, mg/100 ml	6.97(0.17)	7.04(0.16)	7.07(0.15)	6.93(0.15)	7.29(0.17)
Potassium, mEq/liter	4.29(0.05)	4.31(0.04)	4.35(0.05)	4.25(0.04)	4.31(0.07)
Creatinine, mg/100 ml	1.22(0.02)	1.22(0.02)	1.20(0.02)	1.23(0.03)	1.21(0.02)

*Abbreviations for drugs included in the standard regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

†Standard auscultatory method using a mercurial sphygmomanometer.

sure was below the lower limit for entry in 51 and was above the upper limit in 39 patients. Thirty-eight patients were excluded for other reasons.

The characteristics of the 450 patients who were included in the trial are shown in Table 2. It can be seen that there were only minor and generally insignificant differences between treatment groups with respect to age, weight, blood pressure, heart rate, and levels of serum uric acid, potassium, and creatinine.

Table 3.—Initial Diastolic Blood Pressures by Therapeutic Regimen for 383 Patients Completing Six Months of Study

Diastolic Blood Pressure,* mm Hg	Patients per Regimen†				
	R+T	P	P+T	P+H	P+T+H
90-94	20	25	25	23	25
95-99	30	27	28	26	17
100-104	18	20	16	21	21
105-109	7	9	8	5	12

*These figures are an average of three readings each visit for the two last prerandomization visits of the fifth-phase diastolic blood pressure taken in the sitting position with the Arteriosonde.

†Abbreviations for drugs included are R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

Initial Blood Pressure

The distribution of average prerandomization sitting diastolic blood pressures recorded by automated device for the 450 patients included in the study indicated that 89% had pretreatment levels below 105 mm Hg. On the basis of the fourth-phase diastolic blood pressure, the distributions were 55% below 105 mm Hg and 45% at 105 mm Hg or higher.

The automated device, however, provided significantly lower diastolic readings than the auscultatory method. On the basis of readings obtained at the randomization visit, 42% of patients exhibited diastolic readings of 105 mm Hg or higher with the auscultatory method, as compared to 11% with the Arterios automated device. The mean difference in diastolic blood pressure by the two methods was 5.5 mm Hg (SE 0.3).

The average diastolic blood pressures measured during the last two prerandomization visits of the 383 patients who completed six months of treatment are shown in Table 3. The distributions of initial systolic and diastolic blood pressure levels among the various therapeutic regimens were quite similar.

Changes in Blood Pressure

At Six Months.—The method of analysis was to compare the percent of patients on each regimen who achieved the therapeutic goal of a diastolic blood pressure below 90 mm Hg and at least 5 mm Hg less than the initial pressure. The average of the fifth-phase diastolic blood pressure recorded in the sitting position with the automated device at the fifth- and sixth-month visits was used for the posttreatment value (Table 4 and Figure).

The highest percentage response was obtained with the three-drug regimen (P+T+H), where 92% achieved the therapeutic goal. This was followed closely in effectiveness by the regimen R+T, with 88% achieving responses at the endpoint. The least effective regimen was propranolol alone, with only 52% attaining the therapeutic goal. The regimens of intermediate effectiveness were P+T (81% effective) P+H (72% effective).

In comparing the effectiveness of the varous propranolol regimens with the reference (R+T) regimen the significant differences were as follows: propranolol alone was less effective than R+T ($P < .01$) as also was P+H ($P < .05$). The P+T and P+T+H regimens were not significantly different from R+T.

The average automated device pretreatment and posttreatment diastolic blood pressures for each regimen and the reduction in diastolic blood pressure are also shown in Table 5. These mean changes probably are influenced by the fact that dosages of the more effective propranolol regimens were not increased when the therapeutic goal had been attained. Again, the greatest average reduction was obtained with P+T+H followed in order by R+T, P+T, P+H and finally by propranolol. The most effective regimen provided twice as great an average reduction (18.3 mm Hg) as the least effective regimen (9.0 mm Hg).

Table 4.—Patients Attaining Therapeutic Goal*

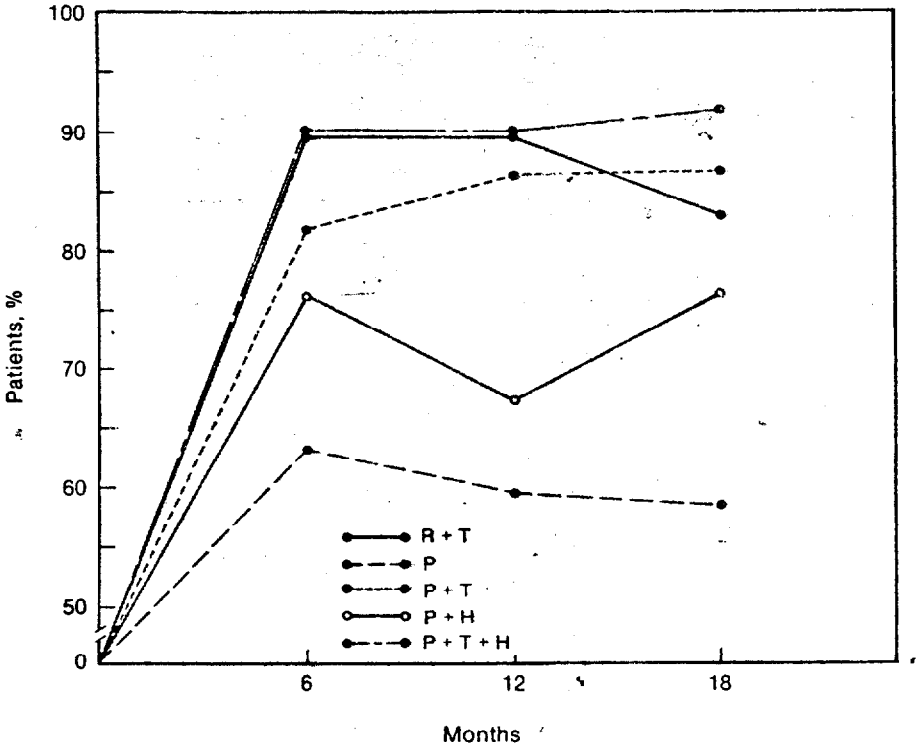
Diastolic Blood Pressure, mm Hg	Regimen† R+T No.	R+T %	P No.	P %	P+T No.	P+T %	P+H No.	P+H %	P+T+H No.	P+T+H %
<90	66	88	42	52‡	62	81	54	72§	69	92
SE		3.8		5.6		4.5		5.2		3.1
90+	9		39		15		21		6	

*Diastolic blood pressure averaging below 90 mm Hg and at least 5 mm less than initial level after 6 months of treatment.

†Indications for the regimen are R+T, reserpine and hydrochlorothiazide; P, propranolol; P+T, propranolol and hydrochlorothiazide; P+H, propranolol and hydralazine; P+T+H, propranolol hydrochlorothiazide, and hydralazine.

‡Significantly different from R+T ($P<.01$).

§Significantly different from R+T ($P<.05$).



Percent of patients achieving diastolic blood pressure below 90 mm Hg and at least 5 mm Hg less than initial blood pressure (fifth phase automated device) at 6, 12, and 18 months following treatment. Various therapeutic regimens are reserpine plus hydrochlorothiazide, R + T; propranolol alone, P; propranolol and hydrochlorothiazide, P + T; propranolol and hydralazine, P + H; propranolol, hydrochlorothiazide, and hydralazine, P + T + H.

Table 5.—Average Systolic and Diastolic Blood Pressures (mm Hg) Before and After Six Months of Treatment

	R+T* (n=75)	P (n=81)	P+T (n=77)	P+H (n=75)	P+T+H (n=75)
Standard					
Before†	151.2	149.5	151.0	150.1	150.3
After‡	124.6	137.9	126.3	135.2	122.8
Reduction	26.6	11.6	24.7	14.9	27.5
SE	1.5	1.8	1.9	1.6	2.2
Fifth phase					
Before	97.7	97.7	97.4	97.3	98.1
After	81.0	88.7	82.9	84.6	79.8
Reduction	16.7	9.0	14.5	12.7	18.3
SE	0.9	1.2	0.9	1.0	0.9

*Abbreviations for drugs included in regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

†Averages of three readings per visit taken with the Arteriosonde at the last two prerandomization clinic visits with the patient sitting.

‡Averages of three readings per visit taken in the same manner at the fifth and sixth month postrandomization.

The relative rankings of the various regimens with respect to effectiveness in reducing diastolic blood pressure were maintained also with respect to systolic blood pressure (Table 5). The range of the reductions as shown in Table 5 varied from a mean fall of 11.6 mm Hg with propranolol alone to 27.5 mm Hg with the P + T + H regimen.

At 12 and 18 Months.—Because of reduced sample size, the 12- and 18-month results do not have the statistical validity of the six-month data. The results for the 228 patients completing 18 months of the trial and attaining the therapeutic goal at 6, 12, and 18 months are shown in Table 6. Although, there are minor changes with the passage of time, the various regimens maintained their comparative ranking as to effectiveness at both the 12- and 18-month intervals, except for P + T, which was slightly more effective at 18 months than R + T.

The six-month analysis is based on the averaging of the fifth- and sixth-month postrandomization blood pressure readings, whereas the 12th- and the 18th-month analyses are based on blood pressure readings taken during the 12th- and 18th-month postrandomization visit only.

Comparison of Readings

The average systolic blood pressures obtained in a sitting position by the two methods automated device and standard ausculatory were quite similar in each of the various regimens both before and after six months of treatment (Table 7). Indeed, the greatest difference between any of these averages was less than 3 mm Hg.

Using the sitting-position, fifth-phase diastolic blood pressure, however, a systematic difference was observed between the automated device and auscultatory readings in that the latter averaged higher. For the pretreatment values, the difference in the readings for the two methods averaged 5.6 mm Hg (SE 0.4). This shifted the distribution to the right, in that by the auscultatory method 82% of the readings fell in the range of 95 to 114 mm Hg prior to randomization. A similar difference was noted in the readings taken six months after randomization. The

Table 6.—Percent of Patients Attaining Blood Pressures* Averaging Below 90 mm Hg and at Least 5 mm Hg Less Than Initial Pressure

Regimen†	6 Months		12 Months		18 Months	
	Arteriosonde	Auscultation	Arteriosonde	Auscultation	Arteriosonde	Auscultation
R+T (n=46)	89.1	71.7	89.1	63.0	82.6	65.2
P (n=43)	62.8	20.9	59.5	28.6	58.1	39.5
P+T (n=44)	81.8	52.3	86.0	60.5	86.4	70.5
P+H (n=46)	76.1	50.0	67.4	47.8	76.1	52.2
P+T+H (n=49)	89.8	71.4	89.4	72.3	91.8	79.6

*Diastolic recorded at fifth phase with patient sitting.
†Abbreviations for drugs included in regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

mean reductions in diastolic blood pressure tended to be slightly, but not significantly, lower by the auscultatory method. Also, the percentage of patients attaining the therapeutic goal after six months of treatment as determined by the auscultatory method was less than by the automated device method (Table 5). This result is to be expected, however, because the auscultatory technique provided higher diastolic readings. Nevertheless, whether the mean diastolic blood pressure reductions or the percentage of patients achieving the therapeutic goal was used as the criterion of effectiveness, the relative rankings of the various regimens remained the same using either the auscultatory or the automated device readings.

Table 7.—Average Pretreatment and Posttreatment Blood Pressures (mm Hg) in 383 Patients

	Regimen*				
	R+T	P	P+T	P+H	P+T+H
Systolic					
Arteriosonde					
Pretreatment	151.2	149.5	151.0	150.1	150.3
Posttreatment	124.6	137.9	126.3	135.2	122.8
Reduction	26.6	11.6	24.7	14.9	27.5
Auscultatory					
Pretreatment†	152.2	151.1	152.3	152.2	153.3
Posttreatment	125.8	139.7	129.5	137.0	124.9
Reduction	26.4	11.4	22.8	15.2	28.4
Diastolic (fifth phase)					
Arteriosonde					
Pretreatment	97.7	97.7	97.4	97.3	98.1
Posttreatment	81.0	88.7	82.9	84.6	79.8
Reduction	16.7	9.0	14.5	12.7	18.3
Auscultatory					
Pretreatment†	103.4	103.8	102.7	102.5	103.9
Posttreatment	87.2	95.7	88.7	92.0	86.0
Reduction	16.2	8.1	14.0	10.5	17.9

*Abbreviations for drugs included in regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.
†Only one prerandomization blood pressure was recorded with sphygmomanometer; whereas the average of two prerandomization blood pressures was recorded with the Arteriosonde.

Changes in Heart Rate

The mean changes in heart rate are shown in Table 8. The mean initial values for the 383 patients completing six months of therapy were similar in the different regimens, varying from 77.1 beats per minute on R+T to 78.7 beats per minute on P+T. All treatments resulted in a reduction of heart rate as compared to the pretreatment level, but the greatest changes occurred with the propranolol regimens. At six months, the average decrease with R+T was 5.0 beats per minute, while with propranolol alone, it was 9.1 beats per minute. Quantitatively, similar falls occurred with all of the propranolol combinations, including those containing hydralazine. No patient had a heart rate of 40 beats per minute or slower. Following the early fall in heart rate, there were no significant additional changes at 12 and 18 months. In computing the latter changes, the initial values used were limited to the patients who had completed the respective time intervals.

Table 8.—Mean Decrease in Heart Rate From Initial Value at 6, 12, and 18 Months Postrandomization*

Regimen	6 Months			12 Months			18 Months		
	N	Δ	SE	N	Δ	SE	N	Δ	SE
R+T	75	5.0	1.3	63	3.1	1.6	46	5.1	1.8
P	81	9.1	1.2	55	9.0	1.5	43	9.2	1.8
P+T	77	8.8	1.2	60	8.0	1.2	44	6.3	1.5
P+H	75	8.9	1.3	59	9.7	1.3	46	7.8	1.5
P+T+H	75	5.9	1.1	63	5.8	1.2	49	7.7	1.5

*N indicates number of patients; Δ, decrease in heart rate; and SE, standard error. Abbreviations for drugs included in regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

Losses from Study

The causes for losses during first six months are detailed in Table 9.

The distribution of losses among the various regimens was fairly uniform, varying from a minimum of 11 losses on the propranolol regimen to a maximum of 16 losses on regimen P+T+H.

The total number of losses from the 6th through the 18th month was 51, which was fewer than the number lost during the first six months (67

Table 9.—Losses During First Six Months Following Randomization

Cause	Regimen* R+T	P	P+T	P+H	P+T+H	Total
Default or errors						
Failed to return	5	4	5	3	6	23
Moved or not taking drugs	0	1	2	1	1	5
Other	1	1	0	1	1	4
Fatal events						
Cerebral hemorrhage	0	0	1	0	0	1
Sudden death	0	0	1	0	0	1
Nonfatal events						
Cerebral thrombosis	0	0	0	2	0	2
Transient ischemic attacks	0	1	0	0	1	2
Migraine	0	0	0	1	0	1
Congestive heart failure	1	1	0	1	1	4
Chronic obstructive pulmonary disease	0	0	1	0	1	2
Myocardial infarction	0	0	0	0	1	1
Side effects						
Depression	0	0	0	2	1	3
Rash	1	0	1	1	3	6
Stuffy nose	1	0	0	0	0	1
Dizziness	2	0	0	0	0	2
Impotence	1	0	0	0	0	1
Miscellaneous						
Leg cramps	1	0	1	0	0	2
Chest, back pain	1	0	0	0	0	1
Alcoholism	0	1	0	0	0	1
Bilateral hydronephrosis	0	0	0	1	0	1
Aortic stenosis	0	1	0	0	0	1
Treatment failures						
Diastolic pressure >114 mm Hg	0	1	0	0	0	1
Hypotension	0	0	0	1	0	1
Total	14	11	12	14	16	67

*Abbreviations for drugs included in regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

Table 10.—Distribution of Patients at Various Dosages Six Months After Randomization

"Propaserp" Dose Level†	Regimen* R+T	P	P+T	P+H	P+T+H	Total
½	1	0	1	2	2	6
1	49	21	42	30	53	195
2	11	11	20	11	9	62
3	8	15	8	11	4	46
4	6	34	6	21	7	74

*Abbreviations for drugs included in regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

†Propranolol increases were as follows: level 1=40 mg, level 2=80 mg, level 3=120 mg, and level 4=160 mg each given three times daily. Level ½=20 mg propranolol and was used only in patients who had hypotension on level 1. All levels of reserpine were 0.1 mg three times daily. "Propaserp" refers to the propranolol-reserpine medication group.

patients). The dropout rate was 11.3% for the last 12-month interval, compared with 14.9% during the first six months. The most effective regimens, R+T and P+T+H, had fewer dropouts than the least effective regimens. There were 11 patients who did not report to the clinic and 13 who either moved away or did not take any medication for three weeks or longer. There were 11 terminating morbid events, including one diagnosed as "sudden death" in a patient who had been receiving propranolol alone. In an additional three patients, nonfatal myocardial infarctions developed, and another had a possible myocardial infarct. Two of these patients were taking P+T; one, P+H; and one, P+T+H. The remaining events were one case each of congestive heart failure, pericarditis, second-degree atrioventricular block, ill-defined dyspnea, paresthesias of the leg, and increased intracranial pressure.

The participation of nine patients in the study was terminated because of side effects. Five patients—two of whom were receiving the reserpine regimen—experienced depression. One of the patients who had been receiving P+H committed suicide. The four other reasons for discontinuation included diabetes mellitus, abnormal liver function tests, peptic ulcer disease, and alcoholism. (These had been treated with the regimens P+T, P+T, P, and R+T, respectively.) Finally, the participation of seven patients was terminated because of diastolic blood pressures exceeding 104 mm Hg on two successive clinic visits. All of these patients were receiving the two least effective regimens, with five receiving P and two receiving P+H.

Dose Levels

Whereas the doses of hydrochlorothiazide, hydralazine hydrochloride, and reserpine remained fixed, the doses of propranolol could be increased as needed from 120 (level 1) to 240, 360, and finally 480 mg/day (level 4). A special 20-mg tablet (level ½) was also provided for patients in whom hypotension or severe bradycardia developed when they were taking one of the doses mentioned.

The relatively poor performance of regimens P and P+H could have been due to less aggressive titration of doses with these two regimens. The data reported in Table 10, however, are inconsistent with this explanation. Level 4, the 480 mg/day level of propranolol hydrochloride, was attained in 34 patients on regimen P and 21 on regimen P+H. By contrast, level 4 was reached in only six patients on regimen P+T and seven patients on P+T+H. It is also evident that the number of patients receiving maintenance therapy at the initial dose level was in direct proportion to the effectiveness of each regimen (Table 9). Thus, 53 (72%) of the patients receiving P+T+H were maintained at the first dosage level, followed in order by 49 (65%) receiving R+T, 42 (55%) receiving P+T, 30 (40%) receiving P+H, and only 21 (26%) receiving propranolol alone.

Side Effects

Biochemical.—Reductions of serum potassium levels and elevations of serum uric acid levels occurred with the

Table 11.—Percent of Patients Showing Abnormal Levels of Serum Potassium and Uric Acid

	Regimen*				
	R+T	P	P+T	P+H	P+T+H
Serum K <3.2 mEq/liter					
Baseline at 6 months	4.0	1.2	0.0	2.6	1.3
	9.3	2.4	10.3	1.3	9.3
Serum uric acid >8.9 mg/100 ml					
Baseline at 6 months	9.3	8.6	10.3	6.6	17.3
	37.3	3.7	28.5	5.3	28.0

*Abbreviations for drugs included in regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

Table 12.—Patients Complaining of Given Side Effect During Six-Month Postrandomization Trial

	Regimen*					
Symptom	R+T	P	P+T	P+H	P+T+H	Total
Headache	17	26	14	24	21	102
Vertigo	22	20	21	13	21	97
Nasal stuffiness	31	21	14	13	18	97
Lethargy	22	13	21	17	18	91
Dyspnea	17	19	8	15	7	66
Altered bowel habits	8	14	14	16	8	60
Joint pain	13	11	16	12	7	59
Ulcer symptoms	8	12	7	11	12	50
Impotence	8	6	11	9	14	48
Palpitations	7	11	11	8	8	45
Angina	8	13	7	9	7	44
Nightmares	6	10	8	5	4	33
Rash	9	4	5	5	9	32
Wheezing	5	7	3	8	3	26
Depression	5	4	2	7	7	25
Syncope	4	5	7	2	3	21
Fever	4	7	2	1	7	21
Other	28	26	30	33	36	153
Total	**222**	**229**	**201**	**208**	**210**	**1,070**

*Abbreviations for drugs included in regimens are as follows: R, reserpine; T, hydrochlorothiazide; P, propranolol hydrochloride; and H, hydralazine hydrochloride.

three regimens containing hydrochlorothiazide (Table 11). The percentage of patients having serum potassium levels below 3.2 mEq/liter varied between 0% and 4% in the different regimens prior to randomization. At six months postrandomization, the incidence of hypokalemia remained at a level of 2.4% for regimen P and 1.3% for regimen P+H. For other regimens, however, the incidence ranged between 9.3% and 10.3%. This trend assumes greater significance when one considers that a few patients in whom hypokalemia developed received supplemental potassium chloride.

Serum uric acid levels of 9 mg/100 ml or higher (determined by an automated system of chemical analysis) prior to randomization were noted in 6.6% to 17.3% of patients (Table 11). Following randomization, elevation of uric acid levels to 9 mg/100 ml or higher occurred in the three regimens that contained hydrochlorothiazide, with the incidence varying between 28% to 37%. There were, however, no recognized cases of acute gout. Again, these values have added significance in view of the fact that some patients received treatment for hyperuricemia.

Subjective.—The most frequent complaints were headache, vertigo, nasal stuffiness, and lethargy (Table 12). More patients on the R+T regimen complained of nasal stuffiness than did patients on other regimens. Otherwise, there did not appear to be a preponderance of one regimen over the others with respect to the various complaints, whether elicited or volunteered. Impotence was complained of with about equal frequency for all regimens. Symptoms of depression also were elicited for all regimens, but they were of mild degree, not justifying removal from the study except in the instances already noted under "losses." Depression was no more frequently complained of in the reserpine-treated patients than in the propranolol-treated patients. Lethargy also was complained of no more frequently with R+T than with the other regimens, except for P. These results demonstrate the lack of specificity in detecting significant subjective side effects by the methods used for this study population.

The advantages of propranolol as an antihypertensive agent[5,6] are said to include relative freedom from disturbing side effects such as lethargy, nasal stuffiness, and impotence that may occur with reserpine therapy. With the possible exception of nasal stuffiness, however, these differences were not apparent in the present study. In fact, depressions occurred as frequently with the propranolol as with the reserpine regimens. This failure to observe fewer side effects with propranolol than with reserpine may be due either to the population seen in the various clinics or to the lack of specificity and gross misrepresentation of side effects that can occur when the patients are asked to respond to a side effects questionnaire. However, the same lack of specificity was found when the analysis was limited to volunteered reports of side effects.

The advantages of reserpine over propranolol are that no titration procedure is required and the expense of treatment is considerably less. The recent claim that reserpine induces breast cancer[9] now appears to be disproved.[10] In the former Veterans Administration trials[1-3,4] as well as in the present study, reserpine has proved to be a consistently effective antihypertensive agent when combined with thiazides and was no more toxic than other antihypertensive drugs. Although this low incidence of severe side effects may not hold in other populations, the reserpine-thiazide combination, when subjected to controlled clinical trials, has uniformly demonstrated antihypertensive effectiveness equal or superior to that of other antihypertensive agents.[1,11,12]

The effectiveness of an antihypertensive drug regimen should be judged not only on the basis of effectiveness and toxicity, but also with respect to the simplicity of dosage and frequency of administration. Propranolol given alone was unsatisfactory by several of these criteria. First, it has poor antihypertensive effectiveness. Despite the fact that doses were raised as high as 480 mg in many patients, hypertension was still poorly controlled. Much higher doses of propranolol than were given in the present study have been used by Prichard and Gilliam,[13] with apparently good effect. However, such huge doses might increase toxicity and would require large numbers of tablets each day. On the whole, it would seem that combination therapy represents a more practical approach. Second, because high doses were required in many instances, this necessitated a somewhat complicated and protracted period of titration. Third, at least three doses per day are required, which is often inconvenient for the patient, who must remember to interrupt his normal daytime activities in order to take medication. Therefore, we do not believe that propranolol alone should be used as the drug of choice in treating hypertension, as has been recommended by at least one authority.[14]

The effectiveness of propranolol was considerably improved when it was combined with the thiazide and was even further improved when it was combined with a fixed-dose combination of the thiazide and hydralazine. Not only was antihypertensive effectiveness increased, but the need for titration was considerably reduced, since most patients responded to the initial or second-step dose of these combinations. Terminating events and side effects were not significantly different with the drug combinations as compared to propranolol alone. Therefore, if propranolol is to be used, it would appear advisable to add it to the regimen of patients who are already taking a thaizide but whose hypertension has not been satisfactorily controlled. Hydralazine could be added later if needed. However, a reserpine-hydrochlorothiazide combination is equally effective, requires no titration, needs only once or twice daily dosage, and is considerably less expensive.

It was anticipated that the combination of propranolol plus hydralazine would be particularly effective because it combines the antihypertensive effects of reduced total peripheral resistance and lowered cardiac output. However, this combination and propranolol-hydrochlorothiazide were less effective than the standard regimen. This emphasizes the importance of the thiazide diuretics not only for basic treatment but also for enhancing the activity of other antihypertensive agents. While the mechanisms of the antihypertensive effects of thiazides have not been completely clarified, it would appear that the volume of total extracellular fluid plays an important role in the pathogenesis of some forms of hypertension[15] and in responsiveness to antihypertensive drugs. Most, if not all, antihypertensive agents other than diuretics are associated with expansion of the extracellular fluid volume. Such volume expansion leads to reduced antihypertensive responsiveness, whereas reduction of volume with diuretics results in enhanced responsiveness.[15] Thus, of the various adjuncts used to enhance the antihypertensive activity of propranolol, thiazides seem to be the most important, although hydralazine also contributes.

Participants

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